

# **EXHIBIT A65**

## ARTICLE

# Perineal Powder Use and Risk of Ovarian Cancer

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- Background** Case-control studies have reported an increased risk of ovarian cancer among talc users; however, the only cohort study to date found no association except for an increase in serous invasive ovarian cancers. The purpose of this analysis was to assess perineal powder use and risk of ovarian cancer prospectively in the Women's Health Initiative Observational Study cohort.
- Methods** Perineal powder use was assessed at baseline by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use. The primary outcome was self-reported ovarian cancer centrally adjudicated by physicians. Cox proportional hazard regression was used to estimate risk, adjusting for covariates, including person-time until diagnosis of ovarian cancer ( $n = 429$ ), death, loss to follow-up, or September 17, 2012. All statistical tests were two-sided.
- Results** Among 61 576 postmenopausal women, followed for a mean of 12.4 years without a history of cancer or bilateral oophorectomy, 52.6% reported ever using perineal powder. Ever use of perineal powder (hazard ratio [HR]<sub>adj</sub> = 1.06, 95% confidence interval [CI] = 0.87 to 1.28) was not associated with risk of ovarian cancer compared with never use. Individually, ever use of powder on the genitals (HR<sub>adj</sub> = 1.12, 95% CI = 0.92 to 1.36), sanitary napkins (HR<sub>adj</sub> = 0.95, 95% CI = 0.76 to 1.20), or diaphragms (HR<sub>adj</sub> = 0.92, 95% CI = 0.68 to 1.23) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use. Estimates did not differ when stratified by age or tubal ligation status.
- Conclusion** Based on our results, perineal powder use does not appear to influence ovarian cancer risk.
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In 2013, it is estimated that there will be 22 240 new cases of ovarian cancer and 14 030 ovarian cancer deaths in the United States (US) alone (1). Since the 1960s, there has been speculation that the use of perineal powder is associated with ovarian cancer. In 2006, the International Agency for Research on Cancer (IARC) reviewed studies examining perineal powder use and ovarian cancer and classified talc as a possible carcinogen (2,3). The proportion of US women ever using talc powder on the perineum was estimated in 2001 to be approximately 40% (4), whereas 52% reported ever use of perineal powder in 1993–1998 within the Women's Health Initiative (WHI) (5).

The primary proposed mechanism linking perineal powder use to ovarian cancer is an inflammatory response (6). Talc particulates from perineal application have been shown to migrate to the ovaries (6), disrupting the surface ovarian epithelial tissue leading to entrapment of the talc particles within inclusion cysts (7). Furthermore, tubal ligation and/or hysterectomy, which would eliminate the pathway of talc particulates to the ovaries, are associated with reduced ovarian cancer risk (6).

A meta-analysis examining the risk of ovarian cancer among ever perineal powder users vs non-users showed odds ratios (ORs)

of 1.40 (95% confidence interval [CI] = 1.29 to 1.52) for population-based case-control, 1.12 (95% CI = 0.92 to 1.36) for hospital based case-control, and 1.35 (95% CI = 1.26 to 1.46) for all case-control studies (2). More recently, a large pooled analysis found that ever use of perineal powder increased epithelial ovarian cancer risk by 24% compared with non-use (OR = 1.24, 95% CI = 1.15 to 1.33) (8). Increased risk was associated with invasive serous, endometrioid, clear cell, and borderline serous subtypes of epithelial ovarian cancer (8). However, when looking at the lifetime number of applications of perineal powder, there was no statistically significant trend for increasing applications, attributed to difficulty in recalling details of frequency and duration of perineal powder use (8).

To date there has only been one prospective study conducted examining perineal powder use and risk of ovarian cancer (9). In the Nurses' Health Study (NHS) cohort, no overall association was found between ever use of perineal powder and epithelial ovarian cancer (relative risk [RR] = 1.09, 95% CI = 0.86 to 1.37) or serous ovarian cancers (RR = 1.26, 95% CI = 0.94 to 1.69) (9). However, there was a 40% (95% CI = 1.02 to 1.91) increase in risk for serous

invasive ovarian cancer with ever perineal powder use, which comprises 86% of serous ovarian cancers in this cohort (9).

Limitations of recall bias and misclassification make it difficult to determine the true relationship between perineal powder (10), a commonly used cosmetic product, and ovarian cancer, a disease with poor survival and few known modifiable risk factors. The prior prospective cohort study, which should not be affected by recall bias, had no information on duration of use limiting interpretation. Here we expand on the available evidence by assessing perineal powder use and risk of ovarian cancer in the Women's Health Initiative Observational Study (WHI-OS). The WHI-OS is a large cohort that collected information on several application areas of perineal powder use and their respective durations of use.

## Methods

### Study Population

The WHI-OS enrolled 93 676 women from 40 clinical centers across the United States from 1993 to 1998 (11). Women were eligible if they were aged 50 to 79 at enrollment, postmenopausal, and planned to reside in the area for at least three years (11). Women were excluded from the WHI-OS if they were participating in another clinical trial, unlikely to survive three years due to medical conditions, or had conditions that would interfere with study participation (11). Participants completed annual mailed questionnaires to update information on risk factors and outcomes, including ovarian cancer (11). Written informed consent was obtained from participants, and all clinical centers were approved by their respective institutional review boards (11). The current analysis was approved by the University of Massachusetts, Amherst Human Subjects Review Committee.

For this analysis, participants were additionally excluded if they reported a bilateral oophorectomy or an unknown number of ovaries at baseline ( $n = 20\,960$ ), a history of any cancer at baseline except nonmelanoma skin cancer ( $n = 10\,622$ ), or were missing exposure or follow up information ( $n = 516$ ). After applying the exclusion criteria, 61 576 participants with 429 adjudicated incident ovarian cancer cases remained.

### Exposure Ascertainment

Perineal powder use was assessed via self-report at baseline. Participants were asked, "Have you ever used powder on your private parts (genital areas)?" Those who responded yes further indicated the duration of use with the following possible responses: less than 1 year, 1–4 years, 5–9 years, 10–19 years, or 20 or more years. For persons that reported ever use of a diaphragm, participants were asked, "Did you ever use powder on your diaphragm?" and those who responded yes further indicated duration. The third category evaluated was "Did you ever use powder on a sanitary napkin or pad?" with those responding yes also reporting duration. Each area of application variable was assessed dichotomously and the duration of use, collapsed into fewer categories because of small numbers, was assessed categorically as never, 9 years or less, or 10 or more years. A combined ever perineal powder variable and duration variable for any powder use was created; where ever use was defined as report of ever use of any of the three application categories, never was report of never use for all three categories,

and duration was the maximum duration reported of any single area of application, because we could not exclude the possibility that applications were concurrent. Lastly, all possible combinations of the three application areas were assessed.

### Outcome Ascertainment

Ovarian cancer cases were initially self-reported by participants in the WHI-OS on annual questionnaires. Medical records, including hospital discharge summaries and pathology reports, were requested for each self-reported case and adjudicated by a physician at the local Clinical Center and then centrally by the WHI's Clinical Coordinating Center (11).

### Covariate Ascertainment

Potential covariates considered included age, race, education, alcohol servings per week, smoking status, metabolic equivalent (MET) hours per week of recreational physical activity, Body Mass Index (BMI), and self-reported family history of ovarian or breast cancer. Reproductive factors considered were age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, history of hysterectomy, history of irregular cycles, history of endometriosis, duration of oral contraceptive use, and duration of postmenopausal hormone use. All covariates were from baseline and were not updated.

### Statistical Analysis

To estimate the association between perineal powder use and ovarian cancer, proportional hazard regression models were used. Participants contributed person-time until diagnosis of ovarian cancer, death, loss to follow-up, or September 17, 2012, whichever came first. Participants with other cancers were still considered at risk for ovarian cancer and were not censored at the time of other cancer diagnoses. Information on incident oophorectomy during follow-up was not available and thus participants were not censored in this analysis. The proportional hazards assumption was tested using weighted Schoenfeld residuals.

Covariates were included in the adjusted model according to purposeful selection, where covariates with Wald  $P$  values of .25 or less in age-adjusted models were entered into an initial multivariable model and then each covariate was subsequently tested individually via likelihood ratio tests in order of decreasing Wald  $P$  values. Variables that had  $P$  values of .10 or less during the backwards elimination were kept in the model until a parsimonious model was obtained. Additional variables shown in previous literature (8,9) but not statistically significant in our population were also included in the final multivariable model. Lastly, family history of breast cancer and personal history of endometriosis did not change estimates and were not included in the final multivariable model.

Models fitted included the following independent variables: 1) combined ever perineal powder use, 2) ever powder use by application area (ie, applied to genitals, applied to diaphragm, or applied to sanitary napkins), 3) duration of use by application area, and 4) application area combinations (ie, genital only, diaphragm only, sanitary napkin only, genital and sanitary napkin, genital and diaphragm, diaphragm and sanitary napkin, and all three areas of application). For duration models, test for trend was used to evaluate linear trends across duration categories by modeling the

categories as a continuous variable in the multivariable regression models.

Because powder particles may not reach the ovaries due to tubal ligation and because previous studies have shown a stronger association between powder use and ovarian cancer in women without tubal ligation (4), we separately examined women without tubal ligation. We also stratified by age at baseline, because older women may have had more potential for exposure to talc contaminated with asbestos. Additionally, associations by ovarian cancer histological subtype were evaluated. All analyses were performed using Stata v.12.1 (StataCorp, College Station, TX) and two-sided *P* values of .05 or less were considered statistically significant.

Results

The average age of the participants at baseline was 63.3 years. Participants were followed for a mean of 12.4 years; never powder users were followed for a mean of 12.2 years (range = 0.12 to 17.9 years) and ever powder users were followed for a mean of 12.6 years (range = 0.03 to 18.0). The majority of the participants were white (83.7%), had less than a college degree (56.1%), and were overweight/obese (57.2%). Approximately half (52.6%) of the population reported ever use of perineal powder. Ever powder users were heavier (27.5 kg/m<sup>2</sup> vs 26.5 kg/m<sup>2</sup>, *P* < .0001) and were more likely to have used oral contraceptives (44% vs 36%, *P* < .0001) and/or diaphragms (50.8% vs 37.3 %, *P* < .0001) than never users (Table 1).

Use of powder on the genitals was associated with a 12% increase in the multivariable-adjusted hazard ratio of ovarian cancer (HR<sub>adj</sub> = 1.12, 95% CI = 0.92 to 1.36), though this was not statistically significant (Table 2). Use of powder on sanitary napkins (HR<sub>adj</sub> = 0.95, 95% CI = 0.76 to 1.20) or diaphragms (HR<sub>adj</sub> = 0.92, 95% CI = 0.68 to 1.23) also was not associated with risk. Duration of powder use on the genitals, sanitary napkins, or on the diaphragm was not associated with ovarian cancer; *P*<sub>trend</sub> for years of use: .67, .69, and .67 respectively. Combined ever powder use from any of the three application areas did not show an association with ovarian cancer risk (HR<sub>adj</sub> = 1.06, 95% CI = 0.87 to 1.28). For combined duration of use, which was the longest duration of use among the three areas of application, there was no evidence of an association with risk of ovarian cancer [*P*<sub>trend</sub> for years of use: .77]. Use of powder on genitals, the most common application area, for 20 or more years was not associated with increased risk of ovarian cancer compared with never users (HR<sub>adj</sub> = 1.10, 95% CI = 0.82 to 1.48). In a sensitivity analysis, invasive serous ovarian cancer risk was not increased (HR<sub>adj</sub> = 0.96, 95% CI = 0.65 to 1.41), even in women reporting durations of use greater than 10 years.

There was no evidence of an association between perineal powder use and ovarian cancer risk by category of application (Table 3). Combined ever powder use was not associated with individual subtypes of ovarian cancer (Table 4). The multivariable-adjusted hazard ratio for serous ovarian cancer was 1.16 (95% CI = 0.88 to 1.53). Additionally, duration of combined ever powder use was also not shown to be associated with any subtype of ovarian cancer (results not shown).

The associations of combined ever powder use and ovarian cancer did not statistically differ by tubal ligation status (results not shown). When stratified by age group at baseline, hazard estimates also did not statistically differ (*P*<sub>interaction</sub> = .37); HR<sub>adj</sub> for younger than

Table 1. Characteristics of postmenopausal women according to perineal powder use status (n = 61 285): Women’s Health Initiative Observational Study, 1993–2012

Characteristic, n (%)	Never perineal powder use	Ever perineal powder use
	n = 29 066	n = 32 219
Race		
White	24 006 (82.6)	27 336 (84.8)
Nonwhite	4991 (17.2)	4811 (14.9)
Body mass index category, kg/m <sup>2</sup>		
<25.0	13 056 (44.9)	12 461 (38.7)
25.0–29.9	9734 (33.5)	10 799 (33.5)
30.0 +	5935 (20.4)	8571 (26.6)
Smoking status		
Never	15 347 (52.8)	15 621 (48.5)
Past	11 481 (39.5)	14 339 (44.5)
Current	1912 (6.6)	1881 (5.8)
Duration of oral contraceptive use, y		
Never	17 877 (61.5)	17 954 (55.7)
<5	6241 (21.5)	7858 (24.4)
5 to <10	2528 (8.7)	3270 (10.2)
10 to <15	1650 (5.7)	2125 (6.6)
15+	760 (2.6)	1005 (3.1)
Diaphragm use	10 826 (37.3)	16 353 (50.8)
Tubal ligation	4929 (17.0)	5901 (18.3)
Hysterectomy	6878 (23.7)	8285 (25.7)
Family history of ovarian cancer	606 (2.1)	660 (2.1)
Parity		
0	3687 (12.7)	3769 (11.7)
1–2	9773 (33.6)	11 585 (36.0)
3–4	11 101 (38.2)	12 609 (39.1)
5+	4365 (15.0)	4098 (12.7)
Age at last birth, y		
Never had term pregnancy	6219 (21.4)	6260 (19.4)
< 20	210 (0.7)	324 (1.0)
20–29	9143 (31.5)	11 480 (35.6)
30+	13 011 (44.8)	13 668 (42.4)
Duration of postmenopausal hormone use, y		
Never	13 381 (46.0)	13 880 (43.1)
<5	6498 (22.4)	7546 (23.4)
5 to <10	3783 (13.0)	4567 (14.2)
10 to <15	2688 (9.3)	3128 (9.7)
15+	2716 (9.3)	3097 (9.6)

50 to 59 years = 1.29, 95% CI = 0.91 to 1.82; HR<sub>adj</sub> for those 60 to 69 years = 0.94, 95% CI = 0.70 to 1.26; and HR<sub>adj</sub> for those 70 to 79 years = 1.01, 95% CI = 0.68 to 1.48. When restricted to only whites or to those who had never used oral contraceptives, results were again unchanged.

Discussion

In this large prospective study, ever perineal powder use was not associated with ovarian cancer risk, nor was it associated with ovarian cancer when assessed by area of application, duration of use, or ovarian cancer subtype. While many case-control studies have shown an approximately 24–40% increase in risk of ovarian cancer (2,8) for powder users, we did not find evidence of this association in our large, prospective analysis.

The meta-analysis of 20 case-control studies by Langseth and colleagues found a 35% increase in the odds of epithelial ovarian

**Table 2.** Age and multivariable-adjusted hazard ratios of ovarian cancer by area of perineal powder application (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR		Multivariable HR*	
			(95% CI)	<i>P</i> <sub>trend</sub> †	(95% CI)	<i>P</i> <sub>trend</sub> †
Powder use on genitals						
Never	247	457 855	1.0 (referent)	.63	1.0 (referent)	.67
Ever‡	181	304 867	1.13 (0.93 to 1.37)		1.12 (0.92 to 1.36)	
Less than 9 years	112	173 118	1.24 (0.99 to 1.55)		1.23 (0.98 to 1.54)	
10 or more years	68	129 647	0.98 (0.75 to 1.29)		0.98 (0.75 to 1.29)	
Powder use on sanitary napkins						
Never	336	590 351	1.0 (referent)	.70	1.0 (referent)	.69
Ever‡	93	172 712	0.96 (0.76 to 1.21)		0.95 (0.76 to 1.20)	
Less than 9 years	62	114 305	0.98 (0.75 to 1.28)		0.96 (0.73 to 1.26)	
10 or more years	30	56 174	0.93 (0.64 to 1.35)		0.95 (0.65 to 1.37)	
Powder use on diaphragm						
Never	373	661 239	1.0 (referent)	.78	1.0 (referent)	.67
Ever‡	52	97 714	0.94 (0.70 to 1.25)		0.92 (0.68 to 1.23)	
Less than 9 years	35	67 468	0.93 (0.66 to 1.32)		0.91 (0.64 to 1.30)	
10 or more years	17	29 202	0.99 (0.61 to 1.60)		0.95 (0.58 to 1.56)	
Combined ever powder uses§						
Never	197	361 583	1.0 (referent)	.67	1.0 (referent)	.77
Ever‡	232	404 983	1.07 (0.89 to 1.30)		1.06 (0.87 to 1.28)	
Less than 9 years	135	228 931	1.12 (0.90 to 1.39)		1.09 (0.88 to 1.36)	
10 or more years	97	173 307	1.03 (0.81 to 1.31)		1.02 (0.80 to 1.30)	

\* Adjusted for: Age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m<sup>2</sup> (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children, missing).

† Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models; *P*<sub>trend</sub> was estimated by modeling categories as continuous. All statistical tests were two-sided.

‡ Person-years may not add up; duration information was missing for some.

§ Combined ever powder use is the longest duration of use among the applications to genitals, sanitary napkins, and diaphragms.

**Table 3.** Age and multivariable-adjusted hazard ratios for ovarian cancer by combined categories of powder use (n = 61576): Women's Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Powder Type Used				
No powder	193	355 523	1.0 (referent)	1.0 (referent)
Only genital powder	96	158 130	1.14 (0.90 to 1.46)	1.13 (0.88 to 1.45)
Only diaphragm powder	19	42 367	0.82 (0.51 to 1.32)	0.80 (0.50 to 1.29)
Only sanitary napkin powder	28	50 051	1.04 (0.70 to 1.54)	1.01 (0.68 to 1.50)
Genital and sanitary napkin powder	55	96 173	1.09 (0.80 to 1.47)	1.08 (0.80 to 1.46)
Genital and diaphragm powder	24	29 858	1.49 (0.98 to 2.28)	1.45 (0.95 to 2.23)
Diaphragm and sanitary napkin powder	4	6 858	1.06 (0.40 to 2.86)	1.02 (0.38 to 2.74)
Genital, diaphragm, and sanitary napkin powder	5	18 331	0.51 (0.21 to 1.24)	0.50 (0.21 to 1.22)

\* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided.

Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m<sup>2</sup> (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

cancer among ever perineal powder users compared to never-users (2), and the pooled analysis of eight case-control studies by Terry and colleagues found a 24% increase in the same group (8). Langseth and colleagues did not assess dose-response or risk among subtypes of ovarian cancer (2). Terry and colleagues assessed lifetime applications of perineal powder and found no statistically significant trend with increasing lifetime applications (8). This corroborates our results that there was no statistically significant risk with increasing duration

of perineal powder use, though they were able to capture both frequency and duration (8), whereas we only had duration. Terry and colleagues found elevated risks for invasive serous, borderline serous, endometrioid, and clear cell subtypes of ovarian cancer (8), which we did not observe. One potential reason that case-control studies have found slight increases in risk is the potential for an overestimation of the true association due to recall bias, because the participants are aware of their ovarian cancer status when reporting powder



**Table 4.** Age and multivariable-adjusted hazard ratios for combined ever powder use by subtype of ovarian cancer (n = 61 576): Women’s Health Initiative Observational Study, 1993–2012

Variable	No. of cases	Person-years	Age-adjusted HR*	Multivariable HR*
			(95% CI)	(95% CI)
Seroust†				
Never	87	355 523	1.0 (referent)	1.0 (referent)
Ever	117	404 983	1.18 (0.89 to 1.56)	1.16 (0.88 to 1.53)
Serous Invasive				
Never	80	355 523	1.0 (referent)	1.0 (referent)
Ever	105	404 983	1.16 (0.87 to 1.55)	1.13 (0.84 to 1.51)
Mucinous				
Never	12	355 523	1.0 (referent)	1.0 (referent)
Ever	13	404 983	0.98 (0.44 to 2.14)	1.03 (0.47 to 2.27)
Endometrioid				
Never	13	355 523	1.0 (referent)	1.0 (referent)
Ever	20	404 983	1.39 (0.69 to 2.79)	1.29 (0.64 to 2.61)
Other				
Never	47	355 523	1.0 (referent)	1.0 (referent)
Ever	54	404 983	1.04 (0.71 to 1.54)	1.04 (0.70 to 1.54)

\* Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in cox proportional hazard regression models. All statistical tests were two-sided. Multivariable HR adjusted for: age (continuous), race (white, nonwhite, missing), oral contraceptive duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), hormone replacement therapy duration in years (never, <5, 5 to <10, 10 to <15, 15+, missing), family history (yes, no, missing), age (y) at last birth (never, <20, 20 to <30, 30+, missing), body mass index in kg/m<sup>2</sup> (<25.0, 25.0 to <30.0, 30.0+, missing), smoking (never, past, current, missing), tubal ligation (yes, no, missing), and parity (0, 1 to 2, 3 to 4, 5+, children missing).

† Includes borderline cancers.

exposure. The prospective nature of our study would eliminate the potential for recall bias. Additionally, the case-control studies tended to have a younger population than our study, which included both premenopausal and postmenopausal ovarian cancers (2,8), whereas the WHI cohort consisted only of postmenopausal ovarian cancers. Ovarian cancer that occurs prior to menopause may have a different etiology than ovarian cancer occurring afterwards.

We found similar results to that of the NHS, the only other prospective cohort, which had a similar sample size and number of ovarian cancer cases to our study. Ever use of perineal powder did not appear to be associated with ovarian cancer in the NHS (9), similar to our findings. The results of Gertig and colleagues were also null for use on the genitals and for use on sanitary napkins (9). Additionally, neither our study nor the NHS found associations with serous ovarian cancer, endometrioid, or mucinous ovarian cancers, although subgroup sample size may have reduced statistical power to test these associations. In contrast to our results, the study by Gertig and colleagues found a 40% increase in invasive serous ovarian cancer among ever powder users compared with never powder users (9).

Strengths of our study included large sample size with a substantial number of ovarian cancer cases, a prospective cohort design, good case ascertainment, and detailed information on most ovarian cancer risk factors. We also had information on duration of powder use, qualifiers not available in several earlier studies, including the previous cohort study (2,8,9).

One potential limitation of our analyses includes a lack of information regarding oophorectomy after baseline, which would result in the inclusion of some women not at risk for ovarian cancer in the analytical cohort. However, the impact was likely to be minor, as a previous study in the WHI-OS had reported the number of persons with incident bilateral oophorectomies to be less than 250 (out of more than 90 000 participants) during nearly eight years of follow-up (12). While the prospective nature of the study design

eliminates recall bias, it does not eliminate potential for nondifferential misclassification of the exposure. Women still needed to recall past perineal powder use and duration and thus may have trouble recollecting specifics regarding the use of perineal powder, leading to a bias toward the null. Information regarding powder use was not collected after baseline, and there is potential for never users to begin using powder; however, this is unlikely because the women are postmenopausal, reducing need to use perineal powder on diaphragms or sanitary napkins. We also had no specific data regarding the frequency of powder use in our sample. Frequency of use, as well as duration may influence ovarian cancer risk. We may have been comparing long-term infrequent users with short-term frequent users. If we had frequency of use in addition to the duration, we could have looked at intensity of use, which may be more accurate, and shown a dose response relationship. However, Terry and colleagues did not find a dose response relationship either when taking into account frequency and duration (8).

When restricted to women without tubal ligation status, the estimates for the association between combined ever perineal powder use and ovarian cancer were not increased. While some studies have found stronger associations between powder use and ovarian cancer in women that have not undergone a tubal ligation (4), the results from our study did not support this previous finding. The pooled analysis (8) and the NHS cohort (9) also did not find evidence of stronger associations in women without tubal ligations.

While we had information on duration of use, it is unknown during which years the perineal powder was used. Talc powder had potential for asbestos contamination (13) until 1976, when the Cosmetic, Toiletry, and Fragrance Association required all cosmetic talc products to be free of asbestos (14). Therefore, those using powder prior to 1976 may have been potentially exposed to asbestos, a known carcinogen. The pooled analysis and meta-analysis also included case-control studies not within the United States

(2,8), which potentially have different regulations regarding perineal powder and earlier studies that may have been more likely to include exposure to contaminated perineal powder (2). However, risk estimates in more recent studies are similar to earlier studies (2), reducing the likelihood that confounding by asbestos is driving the findings. Additionally, assuming older women in the cohort could have been exposed longer to perineal powder with potential contamination compared with younger women, we did not see statistically significant differences in risk when stratified by age group, further suggesting asbestos contamination is not a likely explanation.

The WHI-OS queried general perineal powder use rather than talc powder use, and we had no specific information regarding the content of talc in products used, which the previous literature reviewed by IARC suggested to be the possible carcinogen of concern (2). However, the NHS cohort and most studies included within the pooled analyses asked about general perineal powder use as well (2,8,9). In summary, perineal powder use did not appear to be associated with ovarian cancer risk in this large sample of postmenopausal women, even with use for long durations.

## References

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